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# Accepted Manuscript

## Editorial

Single pulse electrical stimulation and high-frequency oscillations, a complicated marriage

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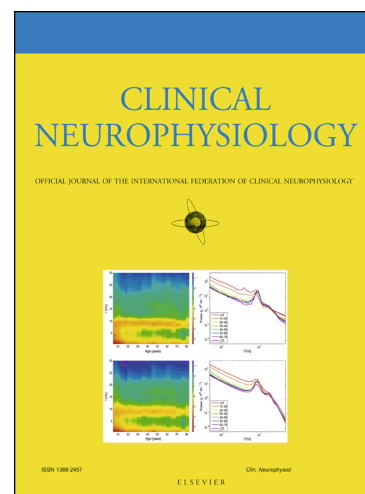
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## Single pulse electrical stimulation and high-frequency oscillations, a complicated marriage

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Since the work from Penfield in the 50s, brain electrical stimulation with trains of pulses has been used mainly to identify functional cortex in patients with intracranial electrodes. Over the last few decades, the study of intracranial EEG responses to single electrical pulses has allowed the identification of brain effective connections and of hyperexcitable cortex involved in seizure generation. This approach has independently been named single pulse electrical stimulation (SPES) and cortico-cortical evoked potentials (CCEPs). A fascinating consequence of this development is that SPES can be used to study cortical and subcortical neuronal networks, either normal or epileptogenic. In order to reach specific objectives, different stimulation parameters, including pulse duration, intensity or stimulation frequency have been used with different protocols at various centers (Donos et al, 2016). For instance, stimulating at 1 Hz can aid in the identification of the seizure onset zone by eliciting the patient's habitual seizures when stimulating the electrode contacts close to the epileptogenic zone (for review, see Kovac et al 2014). Stimulation frequencies between 1 and 0.1 Hz have been used to study effective connectivity between brain areas (Matsumoto et al, 2004; Lacruz et al 2007; Jimenez-Jimenez et al, 2015; Enatsu et al, 2015). Stimulating at low frequencies allows the study of late responses (delayed or repetitive), which appear to be related to the epileptogenic potential of the underlying cortex (Valentín et al., 2005; Flanagan et al., 2009).

SPES has been found to induce high-frequency oscillations (HFOs), including ripples (R) and fast ripples (FR) (van'T Klooster et al., 2011). HFOs in the 100–250 Hz frequency range have been observed in interictal recordings mainly at the seizure onset zone (SOZ) or in areas with high epileptogenic potential (Urrestarazu et al 2007; Engel et al 2009; Jacobs et al., 2010a; Jacobs et al., 2010b). In a recent article, van't Klooster et al. have reported that HFOs evoked by SPES are larger in the SOZ compared with those induced in non-seizure onset areas (van'T Klooster et al., 2017). Similarly, looking at the very early period after SPES (N1), comparing SPES during awake and NREM sleep, Usumi et al have shown that HFOs increase at N1, which is immediately followed by intense inhibition of HFOs. These findings appeared to be greater in the SOZ compared with areas outside the SOZ (Usumi et al 2015).

In this issue of *Clinical Neurophysiology*, Măliia et al. (2017) have further explored the spectral changes at gamma, ripples and fast ripples provoked by SPES at different time windows and at different brain regions. With this new methodological approach, they have categorized three different periods after SPES (10–60, 60–255, 255–500 ms), compared to baseline pre-stimulation periods. As expected by previous published findings, they found a global early excitation of HFOs (10-60 ms). However, they described a delayed inhibition (60-500ms) at different regions, particularly when stimulating primary sensory regions (S1-V1). When comparing different brain regions, SPES in the SOZ induced stronger delayed inhibition than stimulating contacts outside the epileptogenic focus. Interestingly, van't Klooster et al. (2011, 2017) did not identify these periods with HFO inhibitions, probably due to a different methodological approach.

The reasons for the loss of HFO, 60 ms after SPES, are still unclear, and the authors suggest that it could be due to subcortical synchronization mechanisms. However, other possible mechanisms could be considered. The latency periods described for HFO broadly correspond to the initial period of excitation followed by inhibition observed with single cell recordings during SPES (Alarcon et al, 2012), which suggest strong cortical inhibition. New

studies using single cell recordings would be needed to compare between physiological and pathological networks.

Clearly, future work is needed to understand if any particular change in the HFO is related to the generation of late responses to SPES (delayed and repetitive responses). Although delayed responses are similar to interictal epileptiform discharges (Nayak et al, 2014), they are not seen after every identical pulse, and they show slightly different latency periods after each identical stimulus. Studies looking at HFO and late responses are necessary to understand the mechanisms involved in the generation of SPES responses, how spontaneous IEDs are generated in the epileptic brain and their relation to ictal genesis. These excitation/inhibition patterns described in the HFO rhythms and in SPES-induced single cell action potentials are also present in spontaneous interictal epileptiform discharges (Alarcon et al. 2012) and may well be present during particular abnormal or normal EEG patterns.

The report of Mălîia et al. (2017) provides a new insight into the mechanisms involved in HFOs, and can help us understand the cortical dynamics of physiological and pathological brain networks.

### **Conflict of interest**

None of the authors have potential conflicts of interest to be disclosed.

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